EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of a health claim related to citrulline-malate and faster recovery from muscle fatigue after exercise pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to citrulline-malate and faster recovery from muscle fatigue after exercise pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Biocodex, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to citrulline-malate and faster recovery from muscle fatigue after exercise. Citrulline-malate is sufficiently characterised. The claimed effect is "maintenance of ATP levels through reduction of lactates in excess for an improved recovery from muscle fatigue". The target population proposed by the applicant is healthy children above six years of age and adults. The Panel considers that faster recovery from muscle fatigue after exercise contributing to the restoration of muscle function is a beneficial physiological effect. A total of 33 references were considered as pertinent to the claim by the applicant. A number of studies were provided with hospitalised patients or outpatients who presented with various forms of asthenia or fatigue. No conclusions could be drawn from these studies for the scientific substantiation of the claim. No conclusions could be drawn from one study carried out in athletes, owing to the methodological limitations of the study. A number of mechanistic, animal and *in vitro* studies were submitted. In the absence of evidence for an effect of consumption of citrulline-malate on a faster recovery from muscle fatigue after exercise in humans, these studies cannot be used as a source of data for the scientific substantiation of the claim as their results cannot predict the occurrence of an effect of citrulline-malate on recovery from muscle fatigue after exercise *in vivo* in humans. The Panel concludes that a cause and effect relationship has not been established between the consumption of citrulline-malate and faster recovery from muscle fatigue after exercise.

KEY WORDS

Citrulline-malate, muscle fatigue, exercise, health claims

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[1] On request from the Competent Authority of Belgium following an application by Biocodex, Question No EFSA-Q-2011-00931, adopted on 25 April 2012.

[2] Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhäuser-Berthold, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. One member of the Panel did not participate in the discussion on the subject referred to above because of potential conflicts of interest identified in accordance with the EFSA policy on declarations of interests. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen for the preparatory work on this scientific opinion.

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SUMMARY

Following an application from Biocodex, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to citrulline-malate and faster recovery from muscle fatigue after exercise.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and including a request for the protection of proprietary data.

The food constituent that is the subject of the health claim is citrulline-malate, which is a mixture of L-citrulline and D,L-malic acid (1:1) forming a salt. The Panel considers that citrulline-malate is sufficiently characterised.

The claimed effect is "maintenance of ATP levels through reduction of lactates in excess for an improved recovery from muscle fatigue". The target population proposed by the applicant is healthy children above six years of age and adults. The Panel considers that faster recovery from muscle fatigue after exercise contributing to the restoration of muscle function is a beneficial physiological effect.

A total of 33 references were considered as pertinent to the claim by the applicant. These references comprised 18 human studies, four animal studies, seven *in vitro* studies, and four reviews.

The provided reviews contained no primary data which could be used for the scientific substantiation of the claim.

A number of studies were provided with hospitalised patients or outpatients who suffered from physical, psychological or postoperative asthenia, or asthenia during convalescence from an illness, or who complained about fatigue which was not further specified. The Panel notes that the subjects in these studies were (out) patients who presented with various forms of asthenia or fatigue and not with muscle fatigue after exercise. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of a claim on recovery from muscle fatigue after exercise.

To test the impact of citrulline-malate on performance in an anaerobic exercise of high intensity, and on muscle soreness following such exercise, 41 male athletes were randomised to consume a single dose of 8 g citrulline-malate or a placebo one hour before a pectoral training session in a multi-centre double-blind RCT with a cross-over design. The participants underwent a prescribed and standardised training program during which exercises were performed until muscular fatigue. The washout period between the interventions was one week. Subjects were instructed to follow their usual diet over the 2-week study period and not to consume caffeinated beverages on the testing days and the previous two days. The number of repetitions to fatigue was recorded and the subjects were requested to score their muscle soreness 24 and 48 hours after the training session. The differences in the number of repetitions to fatigue between the placebo and the citrulline-malate trial were analysed by within-group factorial 2-way ANOVA. The effect of citrulline-malate on muscle soreness scores was analysed by Wilcoxon signed-rank test. The Panel considers that the statistical analysis did not take into account the repeated measures and the cross-over design of the study (i.e. putative effects of time and order were not addressed). The Panel considers that owing to the methodological limitations of the study no conclusions can be drawn from this study for the scientific substantiation of the claim.

The applicant submitted a number of mechanistic studies and one bioavailability study on citrulline only. The applicant also submitted a number of animal studies (in rats) and *in vitro* studies (in *Euglena gracilis* and in muscle isolated from endotoxemic rats).

The Panel considers that in the absence of evidence for an effect of consumption of citrulline-malate on a faster recovery from muscle fatigue after exercise in humans, these studies cannot be used as a source of data for the scientific substantiation of the claim as their results cannot predict the occurrence of an effect of citrulline-malate on recovery from muscle fatigue after exercise *in vivo* in humans.

The Panel concludes that a cause and effect relationship has not been established between the consumption of citrulline-malate and faster recovery from muscle fatigue after exercise.

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BACKGROUND

Regulation (EC) No 1924/2006[4] harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 25/07/2011.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and including a request for the protection of proprietary data.
- On 31/08/2011, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- The applicant provided the missing information on 13/10/2011.
- The scientific evaluation procedure started on 10/11/2011.
- On 15/12/2011, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The clock was stopped on 22/12/2011 and restarted on 06/01/2012, in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 09/01/2012, EFSA received the requested information as submitted by the applicant.
- On 08/02/2012, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application, and the clock was stopped on 16/02/2012, in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 20/02/2012, EFSA received the requested information as submitted by the applicant and the clock was restarted, in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 23/03/2012, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application, and the clock was stopped on 27/03/2012, in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 03/04/2012, EFSA received the requested information as submitted by the applicant and the clock was restarted, in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

- During its meeting on 25/04/2012, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to citrulline-malate and faster recovery from muscle fatigue after exercise.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: citrulline-malate and faster recovery from muscle fatigue after exercise.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of citrulline-malate, a positive assessment of its safety, nor a decision on whether citrulline-malate is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Biocodex, 7 avenue Gallieni, 94250 Gentilly, France.

The applicant claimed proprietary rights for studies performed on behalf of the applicant and/or using the applicant's product (Bendahan et al., 1997, 2001, 2002; Briand et al., 1986, 1992; Creff, 1982; Dauverchain, 1982; Fornaris et al., 1984; Giannesini et al., 2009; Goubel et al., 1995a, 1995b, 1997; Moinard et al., 2008; Thuillier-Brustion et al., 1990, 1991; Vanuxem et al., 1986, 1990; Verleye et al., 1995) and for information pertaining to the production process of citrulline-malate. For a number of studies the applicant requested confidentiality (Colin, 1972; Commandré, 1973; Creff, 1972; Mande, 1978; Taillade, 1984; Vallat, 1972).

Food/constituent as stated by the applicant

According to the applicant, citrulline-malate.

Health relationship as claimed by the applicant

According to the applicant, citrulline-malate is split after its ingestion into the two moieties L-citrulline and malic acid. L-Citrulline is a key intermediate in the urea cycle, by which mammals excrete ammonia. The applicant claims that this leads to the consumption of NH_4^+, thus limiting the acidosis observed at the muscular level during exercise and acting against the decrease of ATP production. L-Malic acid, a key intermediate in the Krebs cycle, is claimed to be at the origin of ATP production by using the lactate excess during muscular effort.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "maintenance of ATP levels through reduction of lactates in excess for recovery from muscle fatigue".

Specific conditions of use as proposed by the applicant

The target population proposed by the applicant is healthy children above six years of age and adults. The proposed daily dosage of citrulline-malate is 2 g for children and 3 g for adults.

The contents of the ampoule or sachet are to be diluted in a glass of water. Due to the acidity of the product, citrulline-malate should be taken during meals. It should not be consumed during pregnancy and lactation. The duration of consumption should not exceed four weeks. If the feeling of weakness or fatigue persists, a doctor ought to be consulted.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is citrulline-malate, which is a mixture of L-citrulline and D,L-malic acid (1:1) forming a salt.

According to the applicant, the starting materials for citrulline-malate (CAS 54940-97-5) are D,L-malic acid (provided by a supplier) and L-citrulline which is obtained enzymatically from L-arginine by the applicant. D,L-Malic acid and L-citrulline are dissolved in purified water and mixed to yield a 50 % citrulline-malate solution, packaged in ampoules. An alternative dosage form described by the applicant is an effervescent powder, supplied in sachets. Details on the

manufacturing process, composition, batch-to-batch variability and stability information have been provided by the applicant. The content of citrulline-malate in foods can be measured by established methods.

L-Citrulline is a non-proteinogenic alpha-amino acid. It is an intermediate in the urea cycle where it is made from L-ornithine and carbamoyl phosphate. Malate (L-malic acid) is a dicarboxylic hydroxyacid and an intermediate in the citric acid cycle where it is formed by hydration of fumarate. Malic acid contributes to the sour taste of fruits and is also used as a food additive (E296).

The Panel considers that the food constituent, citrulline-malate, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

Initially the claimed effect was described as "citrulline-malate induces two synergic actions: energizing and detoxifying actions that help a rapid reduction of fatigue".

Upon request by EFSA to define better the claimed effect, the applicant indicated that the claim to be considered for evaluation should be "maintenance of ATP levels through reduction of lactates in excess for an improved exercise performance and recovery, in case of tiredness and feeling of weakness".

When informed by EFSA that the claimed effect was still too broad for a scientific evaluation, the applicant provided the following claimed effect: "maintenance of ATP levels through reduction of lactates in excess for an improved recovery after exercise, or in case of tiredness and feeling of weakness".

Following a further request by EFSA for clarification, the claimed effect was defined by the applicant as "maintenance of ATP levels through reduction of lactates in excess for an improved recovery from muscle fatigue". The target population proposed by the applicant is healthy children above six years of age and adults.

The Panel understands that the claimed effect refers to faster recovery from muscle fatigue, and that "maintenance of ATP levels through reduction of lactates in excess" constitutes the mechanism by which citrulline-malate might exert the claimed effect.

Fatigue can be defined as the loss of peak force or power output. Faster recovery from muscle fatigue contributing to the restoration of muscle function (e.g. muscle strength and physical performance) in subsequent exercise bouts or sessions is a beneficial physiological effect.

The Panel considers that faster recovery from muscle fatigue after exercise contributing to the restoration of muscle function is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in PubMed and in the applicant's own archives, using various combinations of the search terms "malate/malic acid", "citrulline", "lactate", "ATP", "NH_3", "ammonium", "energy", "exercise", "muscle", "fatigue", "weakness" and "tiredness". Studies were included if they addressed a relationship between citrulline-malate supplementation and muscular fatigue recovery or physical fatigue improvement, or reported on a potential anti-fatigue mechanism. Studies were excluded if they had health outcomes not considered pertinent by the applicant for the claim, included a specific disease such as diabetes or kidney failure, or were concerned with mechanisms not referring to fatigue.

A total of 33 references were considered as pertinent to the claim by the applicant. These references comprised 18 human studies (including four randomised controlled trials), four animal studies, seven *in vitro* studies and four reviews.

The provided reviews (Curis et al., 2005; Gibala et al., 1997; Rabier and Kamoun, 1995; Vanuxem et al., 1986) contained no primary data which could be used for the scientific substantiation of the claim.

A number of studies were provided with hospitalised patients or outpatients who suffered from physical, psychological or postoperative asthenia, or asthenia during convalescence from an illness (Colin, 1972; Commandré, 1973; Creff, 1972; Dauverchain, 1982; Mande, 1978; Taillade, 1984; Vallat, 1972), or who complained about fatigue which was not further specified (Creff, 1982). The Panel notes that the subjects in these studies were (out) patients who presented with various forms of asthenia or fatigue and not with muscle fatigue after exercise. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of a claim on recovery from muscle fatigue after exercise.

To test the impact of citrulline-malate (CM) on performance in an anaerobic exercise of high intensity, and on muscle soreness following such exercise, 41 male athletes (mean age 29.8 years) who had trained for strength including pectoral workouts for at least six months before the trial were randomised to consume a single dose of 8 g CM or a placebo one hour before a pectoral training session in a multi-centre double-blind RCT with a cross-over design (Pérez-Guisado and Jakeman, 2010). The participants underwent a prescribed and standardised training program during which exercises were performed until muscular fatigue. The washout period between the interventions (CM or placebo) was one week. Subjects were instructed to follow their usual diet over the 2-week study period and not to consume caffeinated beverages on the testing days and the previous two days. The number of repetitions to fatigue was recorded and the subjects were requested to score their muscle soreness 24 and 48 hours after the training session on a scale from 1 to 5. The differences in the number of repetitions to fatigue between the placebo and the citrulline-malate trial were analysed by within-group factorial 2-way ANOVA. The effect of citrulline-malate on muscle soreness scores was analysed by Wilcoxon signed-rank test. The Panel considers that the statistical analysis did not take into account the repeated measures and the cross-over design of the study (i.e. putative effects of time and order were not addressed). The applicant was invited to comment on these limitations of the study and, if feasible, provide a re-analysis of the data. The applicant was also invited to comment on, or provide evidence for, the validity of the questionnaire on the self-reported muscle soreness score. In reply, the applicant informed EFSA that no further evidence could be provided owing to the fact that the study had not been performed by Biocodex. The applicant also informed EFSA that there was no pilot study to validate the muscle soreness questionnaire. The Panel considers that owing to the methodological limitations of the study no conclusions can be drawn from this study for the scientific substantiation of the claim.

The applicant proposed the following mechanisms by which dietary citrulline-malate might contribute to the claimed effect: (1) malate enhances the Krebs cycle and thereby decreases the pyruvate excess; (2) L-citrulline enhances the urea cycle and thereby decreases the NH_4^+ excess (limiting acidosis). The applicant claimed that the combined actions of malate and L-citrulline would thus lead to a sustained ATP production during exercise.

The mechanistic studies submitted by the applicant were related to high-energy phosphate metabolism (Bendahan et al., 1997, 2001, 2002), blood lactate and ammonia kinetics during and after exercise (Fornaris et al., 1984; Vanuxem et al., 1990), blood acid-base balance (Callis et al., 1991), polymorphonuclear neutrophils oxidative burst and nitric oxide production after exercise (Sureda et al., 2009), and branched-chain amino acid utilization during exercise (Sureda et al., 2010). In addition, one bioavailability study on citrulline only was provided (Moinard et al., 2008).

The applicant also submitted a number of animal and *in vitro* studies. The animal studies were carried out in normal (Callis et al., 1991; Giannesini et al., 2011), endotoxemic (Giannesini et al., 2009; Verley, 1995), and old malnourished rats (Osowska et al., 2006). The *in vitro* studies were carried out in *Euglena gracilis* (Briand et al., 1986, 1992; Thuillier-Brustion et al., 1990, 1991) and in muscle isolated from endotoxemic rats (Goubel et al., 1995a, 1995b, 1997).

The Panel considers that in the absence of evidence for an effect of consumption of citrulline-malate on a faster recovery from muscle fatigue after exercise in humans, these studies cannot be used as a source of data for the scientific substantiation of the claim as their results cannot predict the occurrence of an effect of citrulline-malate on recovery from muscle fatigue after exercise *in vivo* in humans.

The Panel concludes that a cause and effect relationship has not been established between the consumption of citrulline-malate and faster recovery from muscle fatigue after exercise.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent, citrulline-malate, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is "maintenance of ATP levels through reduction of lactates in excess for an improved recovery from muscle fatigue". The target population proposed by the applicant is healthy children above six years of age and adults. Faster recovery from muscle fatigue after exercise contributing to the restoration of muscle function is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of citrulline-malate and faster recovery from muscle fatigue after exercise.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on citrulline-malate and faster recovery from muscle fatigue after exercise pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0310_BE). November 2011. Submitted by Biocodex.

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GLOSSARY

ANOVA	analysis of variance
ATP	adenosine triphosphate
CM	citrulline-malate
RCT	randomised controlled trial